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Administration of noncytolytic IL-10/Fc in murine models of lipopolysaccharide-induced septic shock and allogeneic islet transplantation.

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Numerous studies have suggested the potential application of IL-10 as an anti-inflammatory and as an antirejection agent. Unfortunately, cytokines have short circulating t1/2 We developed a murine IL-10/Fc gamma 2a immunoligand that possesses the biologic functions of IL-10 and the long circulating t1/2 in vivo, characteristic of Igs. We mutated the Fc gamma 2a fragment to render the immunoligand ineffective in directing Ab-dependent cell-mediated cytotoxicity and complement-directed cytolysis (noncytolytic IL-10/Fc (IL-10/Fc2-)). In terms of IL-10 activity, IL-10/Fc2- was as effective as rIL-10 mole per mole in preventing lethal septic shock, but the immunoligand had a prolonged period of efficacy in accord with its extended circulating half-life. Contrary to expectations, IL-10/Fc2- treatment tended to accelerate the destruction of islet cell allografts and increase the levels of granzyme B gene expression in local draining lymph nodes. These data suggest that the enhanced cytotoxic activity of allograft-destroying CTLs may contribute to the accelerated allograft rejection. Finally, our studies suggest that a noncytolytic IL-10/Fc fusion protein provides a useful tool to study the biologic effects of IL-10 in vivo and may provide a useful agent for the prevention and treatment of septic shock.

PMID: 7730658, UI: 95248127

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Differential effects of a stem cell factor-immunoglobulin fusion protein on malignant and normal hematopoietic cells.

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Related Resources

We genetically connected the extracellular domain of human stem cell factor to the Fc-portion of human IgG1. The chimeric recombinant stem cell factor IgG1 fusion protein (rSCF-IgG1) had an apparent approximately Mr 190,000 and consisted of three identical covalently linked subunits. It specifically bound to c-kit and the high affinity Fc gamma receptor, respectively. Liquid phase rSCF-IgG1 was, on a molar basis, about eight times more potent than native human rSCF in stimulating the proliferation of c-kit-positive leukemic cell lines and of nonmalignant CD34-positive hematopoietic progenitor cells. Although the effective dose conferring half maximum of [methyl-3H]thymidine uptake by liquid phase and solid phase-bound rSCF-IgG1 were comparable, the plateau level of [methyl-3H]thymidine uptake by malignant cells was decreased by the latter, whereas proliferation of nonmalignant progenitor cells was supported. Liquid phase rSCF-IgG1 had a 2-fold increased potential to maintain primitive nonmalignant progenitor cells in stroma-free long-term culture compared with rSCF. Liquid phase rSCF-IgG1 caused enhanced and prolonged receptor phosphorylation and a more rapid down modulation of c-kit. Our data support the concept that solid phase-attachment of rSCF-IgG1 is sufficient for alteration of biological function and that rSCF-IgG1 partially blocks SCF-stimulated malignant cell growth while supporting normal progenitor cells.

PMID: 10383156, UI: 99310529